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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Application Number: 10/089,995
Filing Date: July 25, 2002
Appellant(s): KIVITS ET AL.

Philip Dubois
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed 16 August 2007 appealing from the Office action mailed 26 February 2007.

(1) Real Party in Interest

A statement identifying by name the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

The examiner is not aware of any related appeals, interferences, or judicial proceedings which will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

(3) Status of Claims

The statement of the status of claims contained in the brief is correct.

(4) Status of Amendments After Final

The appellant's statement of the status of amendments after final rejection contained in the brief is correct.

(5) Summary of Claimed Subject Matter

The summary of claimed subject matter contained in the brief is correct.

(6) Grounds of Rejection to be Reviewed on Appeal

The appellant's statement of the grounds of rejection to be reviewed on appeal is correct.

(7) Claims Appendix

The copy of the appealed claims contained in the Appendix to the brief is correct.

(8) Evidence Relied Upon

Shing et al. Methods in Enzymology. 1987 146:42-48

Belford et al. J of Endocrinology. 1997 154:45-55

Kussendrager et al. 1998. EP 0869134

Quinque et al. 1992, WO 9200014

Kussendrager et al. US 5,596,082

(9) Grounds of Rejection

The following grounds of rejection are applicable to the appealed claims:

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 16-23 and 33-35 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a process for extracting TGF-β and IGF-1 and lactoperoxidase from a milk product comprising the steps of:

a. eluting a basic fraction from a cationic exchange resin with a 0.24M NaCl solution, pH of about 6.5 or a 0.28 M NaCl/10mM ammoniumacetate solution, pH 5.5

b. passing the basic fraction (from step a) over a hydroxyapatite column

c. eluting the hydroxyapatite column sequentially with at least two eluents, said eluents comprising phosphate buffers of increasing salt concentrations wherein the first eluent has a sodium phosphate concentration of 0.05 to 0.2 M and a pH of about 6 and the second eluent has a sodium phosphate concentration of 0.2 to 0.3M and a pH of about 6 or eluting the hydroxyapatite column with at least two eluents said eluents comprising a first eluent comprising 0.12M NaCl/25mM phosphate and a pH of about 7.0 and a second eluent comprising 0.35M NaCl/25mM phosphate and a pH of about 7.0

d. eluting the hydroxyapatite column with a third eluent wherein the eluent has a salt concentration of 0.3 to 0.5M and a pH of 7.0 or a third eluent wherein the eluent has a salt concentration of 1M NaCl/25mM phosphate and a pH of 7.0

thereby eluting, sequentially, fractions enriched for IGF-1, TGF-β, and lactoperoxidase

does not reasonably provide enablement for the full scope of the claims.

The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

The claims are broadly drawn to a method of isolating two specific growth factors, IGF-1, TGF-β, at specifically identified purity, and a third protein, lactoperoxidase, from milk product by a two step process. The process comprises cationic exchange chromatography to isolate a fraction containing all three proteins of interest, and then passing this basic fraction over a hydroxyapatite column and sequentially eluting fractions rich in IGF-1, rich in TGF-β, and rich in lactoperoxidase. The method of recovering a basic fraction from the milk product by cationic exchange chromatography may utilize any, unspecified elution conditions. The second elution process recites a myriad of combinations of salts at a wide range of ionic concentrations and pH gradiants. Without recitation of specific conditions, or a narrow range of conditions, the recited method, which requires the outcome of fractions of specifically identified characteristics comprising:

i. a fraction comprising IGF-1 wherein the ratio of IGF-1 to TGF-β is greater than 10:1

ii. a fraction comprising TGF-β, wherein the ratio of TGF-β to IGF-1 is greater than 5:1,

is merely an invitation to experiment to determine which combinations of conditions would achieve the desired results.

The specification discloses the following method steps:

I. Cationic Exchange Chromatography

The components are eluted with a salt solution buffered at a pH between 5.5 and 7.5. Sodium chloride or potassium chloride is used, but the specification also discloses that other salts e.g. ammonium acetate can be used (page 5, lines 25-29). The specification discloses a pH range from acidic to above neutral pH (between pH 5.5-7.5), a 100-fold range, since the pH scale is a logarithmic one; the disclosure is silent as to the salt concentrations of the eluent.

II. Hydroxyapatite Chromatography

The hydroxyapatite column is eluted sequentially with eluents such as phosphate buffers, sodium chloride and potassium chloride solutions. These eluents must have an increasing salt concentration; alternatively, it is also possible to apply an increasing pH gradient. The specification states that it is preferred that the overall concentration range of salt solutions is between 0.01 to 1.0 M, a hundred-fold range.

a. To obtain an IGF-1 enriched fraction, the column is eluted with a buffer having a pH of 5.5-7 and a phosphate concentration of 0.05-0.2M

b. To obtain a TGF-β enriched fraction, the column is subsequently eluted with a phosphate buffer having a pH of 5.5-7 and a phosphate concentration of 0.2-0.3M.

The specification teaches that these elution steps may entail utilization of a number of different buffers, over a wide range of salt concentrations and a wide range of pH, from acidic to neutral.

c. A further elution step is carried out to recover a lactoperoxidase fraction. The hydroxyapatite column is eluted with a phosphate buffer having a pH of 5.5 to 8 and a phosphate concentration of 0.3 to 0.5 M (page6, lines 12-32). Thus, the specification teaches that this step may be performed with buffers that range from acidic to basic pH.

The working examples disclose the following method steps:

I. Cationic Exchange Chromatography

Isolation of IGF-1, TGF-β, and lactoperoxidase from milk or cheese whey comprises eluting the column with a 0.24M NaCl solution, pH 6.5 (Examples 1 and 2).

The purity of the fraction obtained by ion exchange chromatography can be increased by eluting the fraction with a buffer of 0.28M NaCl/10mM, pH 5.5 (Example 3).

II. Hydroxyapatite Chromatography

Fractions obtained from elution of cationic exchange column are passed over a hydroxyapatite column and eluted with 0.15M phosphate, pH 6.0 to obtain a fraction rich in IGF-1, followed by elution with 0.25M phosphate, pH 6.0 to obtain a fraction rich in TGF-β. A third fraction, rich in lactoperoxidase is obtained by passing an elution buffer of 0.5M phosphate, pH 7.0 over the column (Examples 1 and 2).

An alternative working example is disclosed comprising eluting the IGF-1 rich fraction with a buffer containing 0.20M NaCl/25mM phosphate, pH 7.0, and eluting the TGF-β rich fraction with a buffer containing 0.35M NaCl/25mM phosphate, pH 7.0. The lactoperoxidase rich fraction is obtained by passing a solution of 1M NaCl/25 mM phosphate over the column. The example is silent as to the pH of the elution buffer used in this step of the working example (Example 4).

The narrow range of conditions recited in the working examples contrast with the claims which recite elution buffers comprising a wide range of ionic strength and pH as can be seen in Table below:

Isolation Procedures

	Cationic Exchange Chromatography	Hydroxyapatite Column Elutions		
		Elution 1 IGF-1 rich fraction	**Elution 2** TGF-β rich fraction	**Elution 3** lactoperoxidase
Claims	Recover a basic fraction from the milk product by cationic exchange chromatography	Eluent selected from phosphate buffers, NaCl solutions, KCl solutions, pH 5.5 to 7 and salt concentration of 0.05M to 0.2M	Eluent selected from phosphate buffers, NaCl solutions, KCl solutions, pH 5.5 to 7 and salt concentration of 0.2M to 0.3M	Eluent selected from phosphate buffers, NaCl solutions, KCl solutions, pH 5.5 to 8 and a salt concentration of 0.3M to 0.5M
Working Examples	Recover of basic fraction with 0.24M NaCl, pH 6.5 or 0.28M NaCl/10 mM ammonium citrate, pH 5.5	0.15M phosphate, pH 6.0 or 0.20 M NaCl/25mM phosphate, pH 7.0	0.25M phosphate, pH 6.0 or 0.35M NaCl/25mM phosphate, pH 7.0	0.50M phosphate, pH 7.0 or 1M NaCl/25mM phosphate silent as to pH
Specification	pH 5.5-7.5, NaCl, KCl, other salts, silent as to salt concentrations	Phosphate buffers, 0.05M-0.2M, pH 5.5-7	Phosphate buffers, 0.2M-0.3M, pH 5.5-7	Phosphate buffers, 0.3M-0.5M, pH 5.5-8

The elution buffers disclosed in the working examples vary, in minor ways, over narrow ranges of ionic strength and pH, compared to the breadth of conditions recited in the claims.

(10) Response to Argument

The rejection of claims 16-23 and 33-35 under 35 U.S.C. 112, first paragraph, as not being enabled for the full scope of the claims is traversed by appellant. The reason for the traversal is that the specification provides ample guidance to one skilled in the art as to the selection of eluent buffers, salt concentrations and pH levels needed to practice the claimed invention (page 4 of Appeal brief, last paragraph).

Appellant asserts that the Final Official Action contends that the claimed process must recite specific eluent buffers, salt concentrations and pH levels (page 5 of Appeal Brief, 1st paragraph). The issue is not the recitation of a single specific embodiment, but rather the recitation of reasonable ranges of salt concentrations and pH levels.

With respect to enablement for elution of cationic exchange columns to obtain a basic fraction from milk products:

Appellant argues that both independent claims (claims 16 and 33) recite recovering a basic fraction from a milk product via cationic exchange chromatography; claim 33 recites type of resin to be used, and how the cationic exchange chromatography column is loaded. Appellant asserts that specification provides further guidance (specification, page 5, lines 6-30) as to type of eluent buffers, salt concentrations and pH levels; additionally, the specification refers to US 5,596,082 as providing guidance (page 5 of Appeal Brief, paragraphs 2 and 3). Appellant indicates that publications cited by Examiner in previous Office Action (6 June 2006) indicate that the claimed process is enabled (page 8 of Appeal Brief, 2nd paragraph).

Appellant's arguments have been fully considered but have not been found to be persuasive. The issue under discussion is not how to prepare a cationic exchange column, but what specific elution conditions would result in elution of a fraction enriched for growth factors IGF-1, TGF-β, and lactoperoxidase. While the claims are to be interpreted in light of the teachings of the specification, it is improper to read limitations or embodiments of the specification into a claim (See MPEP 2111.01). While the specification (page 5) discusses a wide range of possible buffers comprising different salts at a range of pH conditions ranging from acidic to alkaline, it is silent as to what salt concentration is to be used in formulating the elution buffers. US 5,596,082 is referenced in the specification (page 5, line 18) as providing guidance for preparation and running of the cationic exchange column, not which buffers are suitable for recovering a basic fraction from a milk product. Thus, the disclosure does not provide sufficient guidance to enable the skilled artisan, without undue experimentation, to select a buffer of appropriate ionic strength and pH, among the myriad of possibilities set forth in the specification. The breadth of the guidance in the specification and

claims constitutes an invitation to experiment. The art cited in the Office Action of 6 June 2006 (1987. Shing et al. Methods in Enzymology, 1997, Belford et al. J of Endocrinology 154:45-55, 1998, Kussendrager et al. EP 0869134, column 6, lines 43-51) is cited to indicate the wide range of specific salt concentrations and pH levels used to elute growth factors from a cationic exchange column. For example, Kussendrager et al. (1998. EP 0869134, cited on IDS of 8 April 2002) teach elution of polypeptide growth factors with a buffer of 0.3M NaCl, pH 6.5, while Shing et al (1987. Shing et al. Methods in Enzymology, cited in Office Action of 6 June 2006) teach elution with a 0.6M NaCl, pH 7.0. The art of record teaches isolation of a fraction from milk products enriched for growth factors by elution from a cation exchange column using specific combinations of salt concentrations and pH. The art cited teaches elution of polypeptide growth factors from a milk product comprising the first step of the claimed invention, recovering a fraction from the milk product by cationic exchange chromatography. The references cited each recite different, specific conditions for elution of a fraction comprising growth factors; therefore, one could not rely on guidance provided in the art of record to supplement the general teachings in the specification of the instant application, which teach a broad range of elution conditions. Thus, one of ordinary skill in the art could utilize only the guidance presented in the working examples 1-3, which recite eluting a basic fraction from a cationic exchange resin with a 0.24M NaCl solution, pH of about 6.5 or a 0.28 M NaCl/10mM ammonium acetate solution, pH 5.5 to predictably obtain a fraction enriched in growth factors to formulate an elution buffer which would be suitable for elution of a basic fraction from the milk product comprising polypeptide growth factors.

With respect to enablement for elution of hydroxyapatite column sequentially to obtain a fraction comprising IGF-1, wherein the ratio IGF-1 to TGF-β is greater than 10:1, a fraction comprising TGF-β, wherein the ratio of TGF-β to IGF-1 is greater than 5:1, and a third fraction comprising lactoperoxidase:

Appellant argues that independent claims 16 and 33 provide guidance as to the initial pH concentrations that are used to practice the claimed invention (page 5 of

Appeal Brief, last paragraph, bridging page 6, 1st paragraph). The specification provides guidance as to preferred type of resin and process parameters. As to eluting the hydroxyapatite column with a third eluent, appellant argues that the skilled artisan would take into consideration the salt concentrations and pH already utilized in the first two buffers (page 6, of Appeal Brief, last paragraph). Appellant asserts that given that two separate fractions having specifically identified characteristics, a fraction comprising IGF-1 wherein the ratio of IGF-1 to TGF-β is greater than 10:1 and a second fraction comprising TGF-β, wherein the ratio of TGF-β to IGF-1 is greater than 5:1, must be obtained, any process parameters or conditions that did not provide these specifically identified characteristics would be excluded from the claims (page 7 of Appeal Brief, last paragraph, bridging page 8, 1st paragraph).

Appellant's arguments have been fully considered but have not been found to be persuasive.

The issue under consideration is not the type of resin to be used or the method of preparation of a hydroxyapatite column. The issue is what elution conditions would result in the three specifically recited fractions: a fraction enriched in IGF-1 wherein the ratio of IGF-1 to TGF-β is greater than 10:1, a fraction comprising TGF-β, wherein the ratio of TGF-β to IGF-1 is greater than 5:1 and a fraction enriched in lactoperoxidase. The claims are drawn to a wide range of buffers; the artisan is to choose from a myriad of buffers made of different combinations of salts, ionic strengths and pH gradients. Insufficient guidance is provided in the specification to allow one of ordinary skill in the art to vary the salt concentrations or pH gradient to achieve the required results; rather this is an invitation to experiment. The elution buffers disclosed in the working examples vary, in minor ways, over narrow ranges of ionic strength and pH, compared to the breadth of conditions recited in the claims (for example, pH 5.5-7). Claims 17 and 33 recite a third eluent selected from phosphate buffers, sodium chloride solutions and potassium chloride solutions identified only as having increased salt content or pH as compared to the first and second eluents, Claim 18 recites a pH ranging from acidic (pH 5.5) to basic (pH 8), a 500-fold range. Since the elution buffers recited in the claims (Claims 16, and 33) to elute required fractions (a fraction enriched in IGF-1 wherein the

ratio of IGF-1 to TGF-β is greater than 10:1, a fraction comprising TGF-β, wherein the ratio of TGF-β to IGF-1 is greater than 5:1), encompass a broad range of salt concentrations and pH, the skilled artisan would be unable to determine a third eluent to elute the lactoperoxidase fraction. While Appellant asserts that any conditions that did not provide the required fractions would be excluded from the claims, insufficient guidance is presented in the specification as to which conditions will work, i.e. will result in elution of the specifically recited fractions. One of ordinary skill in the art could not predict that one would be able to obtain fractions of the specificity recited in the claims without undertaking undue experimentation. Appellant's argument underscores the fact that the claims merely represent an invitation to experiment to determine what combinations of variables would result in a desired outcome.

Appellant asserts that art cited in the Official Action of 30 June 2006, teaching elution of growth factors from milk products (e.g. Belford et al, Kussendrager et al. and Quinque) (page 8 of Appeal Brief, 2nd paragraph) do not cast doubt as to whether the claimed process is enabled. These references each teach isolation of growth factors from milk products utilizing cation exchangers and specifically taught elution buffers. Each reference teaches a different, specific buffer; thus the art cannot be relied upon to supplement the insufficient guidance provided in the specification of the instant application as to elution conditions required to obtain a basic fraction from the milk product by cationic exchange chromatography. The teachings of the prior art do not anticipate a method which would result in the required results: elution of a fraction comprising IGF-1, wherein the ratio IGF-1 to TGF-β is greater than 10:1, a fraction comprising TGF-β, wherein the ratio of TGF-β to IGF-1 is greater than 5:1, and a third fraction comprising lactoperoxidase. The teachings of the art cannot be relied upon to overcome the insufficient guidance provided in the specification as to the first, second and third elution buffers required to elute the hydroxyapatite column to obtain the specifically requied fractions of IGF-1, TGF-β and lactoperoxidase. However, just as the prior art does not enable the result required by the instant claims, the breadth of the instant claims is not commensurate in scope with that same required result.

Regarding appellant's argument that the Examiner has not supported the scope rejection with either rationale or evidence, the assertion that the specification does not enable one of ordinary skill in the art to practice the invention commensurate in scope with these claims is supported by reasoning presented in the Office Actions, as reproduced in the instant Examiner's Answer.

(10) Related Proceeding(s) Appendix

No decision rendered by a court or the Board is identified by the examiner in the Related Appeals and Interferences section of this examiner's answer.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

Shulamith H. Shafer
19 November, 2007

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